Docket No. 20347 (C38435/111656)

PATENT APPEAL

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Date: October 11, 2002

Sheila Chang

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Heinrich BACHMANN *et al.*

Serial No.: 09/504,393

Filed: February 15, 2000

For: **β,β-CAROTENE 15, 15'-DIOXYGENASES, NUCLEIC ACID SEQUENCES CODING THEREFOR AND THEIR USE**

Examiner: Yong Pak

Group Art Unit: 1652

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APPELLANTS' BRIEF ON APPEAL

Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an appeal from the final rejection of all claims which are pending in this application.

In accordance with 37 CFR § 1.192(a), this brief is being submitted in triplicate, together with a check in the amount of $320.00 in payment of the fee required upon filing this brief. 37 CFR § 1.17(c).

Since the Notice of Appeal was accorded a filing date of March 11, 2002, a five-month extension of time is hereby requested and a check in the amount of

10/18/2002 MBERHE 00000053 09504393
01 FC:1402 320.00 OP
02 FC:1255 1960.00 OP

$1960.00 in payment of the fee required for the extension also is submitted herewith. 37 CFR § 1.17(a)(5). Accordingly, this brief is filed timely upon mailing, with an executed Certificate of Mailing, on or before October 11, 2002.

If either check is missing or additional fees are required or a refund is in order, please debit or credit our Deposit Account No. 02-4467 as appropriate.

IDENTIFICATION OF REAL PARTY IN INTEREST

The real party in interest is ROCHE VITAMINS INC., which is the assignee of record of the present application and is a corporation organized and existing under and by virtue of the laws of the State of Delaware. Ownership of ROCHE VITAMINS INC. lies in F. HOFFMANN-LA ROCHE AG., a company organized and existing under the laws of the Swiss Confederation.

RELATED APPEALS AND INTERFERENCES

Upon information and belief of the undersigned counsel, Appellants and the assignee of record are not aware that there are any pending appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

STATUS OF ALL CLAIMS AND AMENDMENTS

A. Status Prior To Final Rejection

As filed, this Application contained claims 1-35.[1/] The claims were subject to a three-way restriction requirement. (Paper No. 8, pp. 2-4). On December 29, 2000,

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1/ As originally filed, the application contained two claims numbered "27." By Examiner's Amendment, beginning with the second occurrence of claim 27, the claims were renumbered 28-36. (Paper No. 8, p. 2, lns. 2-5).

an election was made to prosecute the subject matter of Group II (claims 6-15, 19-32, and 34-36). In Paper No. 8, the Examiner withdrew claims 1-5, 16-18, and 33 from consideration and allowed claims 28-32 and 34-36. (*Id.* at p.1, ¶¶ 4a and 5). In the RESPONSE TO OFFICE ACTION INCLUDING AMENDMENT AND PETITION FOR EXTENSION OF TIME dated July 31, 2001 ("July 31, 2001 Response"), the election was affirmed. (*See* p. 7, lns. 18-19).

In preparing the reply to Paper No. 8, Appellants became aware that the polypeptide identified in the specification as SEQ ID NO:1 had been misnamed. This information was promptly brought to the attention of the Examiner and claims 6, 8, 9, 11, 12-15, 19, 27, 28, and 34-36 were subsequently amended (1) in view of the restriction requirement and (2) so that they no longer recited or depended from a claim that recited "β,β-carotene 15, 15'-dioxygenase." (July 31, 2001 Response, pp. 2-4).

No further amendments were presented prior to final rejection.

B. Status After Final Rejection

Amendments were presented to the claims and claims were added after final rejection, but the amendments and added claims were not entered. (*See* RESPONSE TO OFFICE ACTION INCLUDING AMENDMENT AND PETITION FOR EXTENSION OF TIME dated February 28, 2002 ("February 28, 2002 Response") and Paper No. 14, p. 2, lns. 2-5). In a Supplemental Amendment After Final filed on October 2, 2002, claims 7-9 were cancelled, without prejudice, to reduce the issues on appeal. The Supplemental Amendment was entered by the Examiner. (Paper No. 17).

C. **Identification Of Claims On Appeal**

Claims 6, 10-15, 19-32, and 34-36 are on appeal and are reproduced in APPENDIX I to this brief. We note that the Final Office Action (Paper No. 11, p. 1, ¶6) states that claims 6-36 are rejected; but claims 16-18 and 33 (as well as claims 1-5) were previously withdrawn from consideration. (See Paper No. 8, p. 1, ¶4a).

SUMMARY OF THE INVENTION AND THE CLAIMS

Vitamin A is a biologically active substance that is essential for man and animals. The term "vitamin A" embraces a class of compounds that includes retinal, retinol, 3-dehydroretinol, retinoic acid, isomers of such compounds, and retinylesters. (Specification, p. 1, lns. 14-16).

Vitamin A is formed by converting precursor carotenoids (also called provitamins A) into vitamin A. These carotenoid precursors (including β-carotene) can only be formed in plants, in photosynthetically active microorganisms, and in other microorganisms. Man and animals are able to convert such provitamins A enzymatically into vitamin A. (Specification, p. 5, lns. 13-17).

Thus, attempts have been made to commercially produce vitamin A from carotenoid precursors for many years. The first step in the process was to purify and characterize the enzymes responsible for converting, *e.g.* β-carotene into retinal. Since 1955, many attempts have been made to purify and characterize these enzymes using biochemical methods. (Specification, p. 6, lns. 3-8).

The prior attempts to form retinal (a form of vitamin A) from carotenoid precursors have a number of disadvantages. Most notably, the prior attempts have

purified enzymes having specific activities of no more than 600 pmol retinal formed/mg protein per hour. These specific activities are not commercially useful, and thus have been considered failed attempts. (Specification, p.6, lns. 5-10).

Accordingly, the present invention provides a process for enzymatically converting β-carotene to retinal through the use of an enzyme identified and purified using a combination of biochemical and molecular biological techniques. Using these techniques, a chicken enzyme was purified 226-fold, yielding a specific activity over four times higher than previously reported, *i.e.*, 2,500 pmol/h/mg. From this preparation, a partial amino acid sequence was obtained, which was used to make degenerate PCR primers. (Specification, p. 6, lns. 12-21).

Using the PCR primers, a full length cDNA was identified, cloned, and sequenced. (Specification p. 7, lns. 5-13 and p. 22, lns. 17-19). A recombinantly expressed protein encoded by the cDNA was shown to enzymatically cleave β-carotene to retinal. (Specification p. 25, lns. 9-12 and Figs. 7 and 8).

STATEMENT OF THE REJECTIONS AND ISSUES

Whether claims 6, 10-15, 19-32, and 34-36 are unpatentable under 35 USC §101 as lacking a specific and substantial utility that is credible, and thus also are unpatentable for failing to teach how to use the claimed invention under 35 USC §112, first paragraph.

GROUPING OF CLAIMS

Not all claims stand or fall together.

Arguments are presented below which demonstrate the patentability of claims 6, 10, 11, and 28-32.

Separate arguments are presented which demonstrate the separate patentability of claims 12-15 and 34-36.

Separate arguments are presented which demonstrate the separate patentability of claims 19-27.

SUMMARY OF THE POSITIONS TAKEN BY THE EXAMINER IN THE FINAL OFFICE ACTION

After the first Office Action was issued, Appellants determined that the name given to the polypeptide designated "SEQ ID NO:1" in the specification, namely "β,β-15,15' dioxygenase" was incorrect. This misnaming was identified by the Appellants through subsequent studies of the polypeptide using a more sensitive assay that was developed after the filing date of the application whereby symmetric vs. non-symmetric metabolites of β,β-carotene could be resolved. These subsequent studies revealed that the enzyme disclosed in the application is a β,β-carotene 15, 15'-monooxygenase. (*See* Michele G. Leuenberger *et al.*, "The Reaction Mechanism of the Enzyme-Catalyzed Central Cleavage of β-Carotene to Retinal," *Angew. Chem. Int. Ed.* 2001, 40 No. 14, pp. 2614-2617, attached hereto as Appendix II). All other physical and structural properties disclosed in the application, including the substrate, reaction product, and structures of the nucleotide and polypeptide sequences, are correct. (*See Id.*; and July 31, 2001 Response, p. 4, lns. 17-18).

This information was promptly conveyed to the Examiner and the Examiner's supervisor (Dr. Ponnathapura Achutamurthy) during a series of teleconferences prior to, and again in, the July 31, 2001 Response.

In the Final Action, the Examiner rejected claims 6-36 under 35 USC §101 because the claimed invention "lacks patentable utility."[2/] (Paper No. 11, p. 3, lns. 1-2). In making the rejection, the Examiner asserted that "the claimed polynucleotides are not supported by either a specific and substantial asserted utility." (*Id.*, lns. 2-3). The Examiner further asserted that "the specification does not teach the function of SEQ ID NO:1." (*Id.*, lns. 8-9).

The Examiner also asserted that "the β,β-carotene 15,15'-monooxygenase activity of SEQ ID NO:1 is unpredictable in the art because SEQ ID NO:1 has homology with polypeptides with β,β-carotene 15,15'-dioxygenase activity" and that "[t]hese claims amount to a polypeptide with unknown function and a polypeptide with unknown and unpredictable function has no utility." (*Id.*, lns. 11-13).

The Examiner then concluded that "[t]herefore, there is no specific, substantial, or credible utility that is well known, apparent, or implied by the relationship of the instant polynucleotide to the polynucleotide encoding SEQ ID NO:1." (*Id.*, lns. 13-15).

2/ In making the rejection, the Examiner ignored the fact that she had previously ***withdrawn*** claims 16-18 and 33 (in addition to claims 1-5) from consideration and allowed claims 28-32 and 34-36. We assume for purposes of this appeal that claims 16-18 and 33 are ***not*** part of the Final Rejection because they were withdrawn from consideration in Paper No. 8, and we also assume that the allowance of claims 28-32 and 34-36 has been withdrawn. If our assumptions are incorrect, the Examiner is requested to clarify on the record, which claims are pending and under final rejection and that Appellants be given an opportunity to amend their brief should the previously withdrawn claims be deemed to be part of the final rejection.

The Examiner further rejected claims 6-36 under the enablement provision of 35 USC §112, first paragraph. (Paper No. 11, pp. 3-4). In making the rejection, the Examiner asserted that "[s]ince the claimed invention is not supported by either a specific asserted utility or a well established utility ... one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation." (*Id.* at p. 4).

The Examiner also asserted that "the specification does not teach the function of the polypeptide encoded by SEQ ID NO:2 because the specification does not teach the correct function of the polypeptide. In the state of the art, the function of a polypeptide is unpredictable from its structure and the functionality of a polypeptide must be known in order to use the polypeptide." The Examiner concluded, "[t]herefore, the specification does not teach how to use SEQ ID NO:1 and DNA molecules encoding SEQ ID NO:1 without undue experimentation." (*Id.*).

In the Advisory Action, in response to Appellant's showing that:

> (i) The specification describes at least three utilities for the claimed invention;
>
> (ii) That a compound and all of its properties are inseparable and that a name alone does not impart or depart utility; and
>
> (iii) That only the name of the enzyme was misidentified in the specification, ***not*** its function, *i.e.*, cleavage of β-carotene to retinal;

the Examiner asserted that "[e]xamples 1-6 all relate to detecting activity, cloning, purification and expression of β,β-carotene 15,15'-dioxygenase" and that "[t]he specification does not support utility for a β,β-carotene 15,15'-monooxygenase." The

Examiner then summarily contended that "[i]dentifying a polypeptide as a β,β-carotene 15,15'-monooxygenase does not endow the polypeptide with such a utility. ... [nor does the specification disclose] how to use SEQ ID NO:1 and 3 or DNA molecules encoding SEQ ID NO:2 without undue experimentation." (*See* Paper No. 14, p. 3, lns. 7-11 and p. 4, lns. 2-6).

THE LEGAL STANDARDS

A. 35 USC §101 - Utility

The patent statute requires that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, ..." 35 USC §101.

As is well settled, the question of utility stands or falls with **what is claimed**; it does not extend to unclaimed subject matter. *Carl Zeiss Stiftung v. Renshaw plc.*, 20 USPQ2d 1094, 1100-1101 (Fed. Cir. 1991) (district court's ruling of invalidity of claim 3 based on lack of utility reversed in view of the district court's misinterpretation of the ***claimed*** invention) and MPEP §2107.02 I at 2100-37 (8th Ed. August 2001) ("The ***claimed invention*** is the focus of the assessment of whether an applicant has satisfied the utility requirement.").[3/]

To reject ***claims*** in an application under § 101, an Examiner must show an unrebutted *prima facie* case of lack of utility. *In re Gaubert*, 187 USPQ 664, 666 (CCPA 1975).

The PTO's *prima facie* showing "***must***" contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the

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3/ Unless otherwise stated, emphasis is ours throughout the Brief.

claimed invention is neither both specific and substantial nor well established; (2) support the factual findings relied upon in reaching the conclusion; and (3) evaluate ***all*** relevant evidence of record, including utilities taught in the closest prior art. MPEP §2107.02 IV at 2100-41; Revised Interim Utility Guidelines Training Materials, p. 9; and Revised Interim Utility Examination Guidelines 66 FR 1092, 1098 (January 5, 2001).

There is no *per se* rule for compliance with the statutory requirement of utility under 35 USC §101. The character and amount of evidence that must be provided by an applicant will vary depending upon what is ***claimed*** and whether the asserted utility appears to contradict established scientific principles and beliefs. *Ex parte Ferguson*, 117 USPQ 229, 231 (Bd. App. 1957); *In re Gazave*, 154 USPQ 92, 96 (CCPA 1967); and *In re Chilowsky*, 108 USPQ 321, 325 (CCPA 1956). The applicant does ***not*** have to provide evidence sufficient to establish an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 206 USPQ 881, 883-884 (CCPA 1980) (reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court observed that a rigorous correlation is not necessary when the test is reasonably predictive of the response.). Rather, evidence of an asserted utility is sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is "***more likely than not true***." MPEP §2107.02 VII at 2100-43.

In the absence of a proper *prima facie* case, an applicant who complies with the other statutory requirements is entitled to a patent. *See In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On appeal to the Board, an appellant can

overcome a rejection by showing insufficient evidence of a *prima facie* case by the Examiner. *See Id.*

B. 35 USC §112, First Paragraph - Enablement

The patent statute requires, in relevant part, that "[t]he specification shall contain a written description of the invention and of the manner and process of making and using it, ..." 35 USC §112, first paragraph. To reject a claim under the enablement provision of §112, first paragraph based on lack of utility under §101, an Examiner must show an unrebutted *prima facie* case of lack of utility. *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

In the absence of a proper *prima facie* case, an applicant who complies with the other statutory requirements is entitled to a patent. *See In re Oetiker*, 24 USPQ2d at 1444 and MPEP §2164.07 I.A. at 2100-185 ("A 35 USC §112, first paragraph, rejection should ***not*** be imposed or maintained unless an appropriate basis exists for imposing a rejection under §101.... In particular, the factual showing needed to impose a rejection under 35 USC §101 ***must*** be provided if a 35 USC §112, first paragraph, rejection is to be imposed on 'lack of utility' grounds."). On appeal to the Board, an appellant can overcome a rejection by showing insufficient evidence of *prima facie* lack of enablement. *See In re Oetiker*, 24 USPQ2d at 1444.

SUMMARY OF THE ARGUMENT

The Examiner improperly shifted the burden of establishing an asserted utility that is specific, substantial and credible to Appellants. In doing so, the Examiner (1) failed to evaluate ***all*** relevant evidence of record; (2) failed to set forth the reasoning

used in concluding that the asserted utility for the claimed invention is neither specific and substantial nor well established; and (3) failed to support the findings relied upon in reaching her conclusion with facts. The Examiner also made factual errors on which the rejections are predicated. Consequently, the Examiner failed to make out a *prima facie* case of lack of utility. For the same reasons, the Examiner also failed to meet her burden of establishing a *prima facie* case of non-enablement.

ARGUMENT

POINT I

THE EXAMINER FOCUSED ON AN UNCLAIMED NAME AND FAILED TO FOLLOW PTO PROCEDURE AND IMPROPERLY PLACED THE INITIAL BURDEN ON THE APPLICANT TO DEMONSTRATE UTILITY

As developed in more detail below, the Examiner fixated upon Appellants' disclosure to the PTO that the polypeptide designated as SEQ ID NO:1 in the application was incorrectly ***named***. (*See* July 31, 2001 Response, p. 4, lns. 11-19).

The first error is that the Examiner has not identified any authority that supports a conclusion that merely misnaming a compound is sufficient to establish a lack of utility. Moreover, even if there were such authority, ***a name is not claimed***, a SEQ ID NO is, and the Examiner never addressed or acknowledged (except for entering the claim amendments set forth in the July 31, 2001 Response) the scope of the claims under appeal. Thus, because the Examiner has not come to grips with the scope of the claims and the fact that a name is not claimed, the rejection must be reversed for this reason alone.

The second error is that the Examiner treated the misnaming of SEQ ID NO:1 as a complete admission of non-utility, which it was not, and impermissibly shifted the burden to Appellants to demonstrate utility:

> ***Applicants state*** that subsequent studies revealed the function of the enzyme represented by SEQ ID NO:1 is a β,β-carotene 15,15'-monooxygenase rather than a β,β-carotene 15,15'-dioxygenase.... However, the specification teaches that SEQ ID NO:1 has β,β-carotene 15,15'-dioxygenase activity. Therefore, the specification does not teach the function of SEQ ID NO:1. Further, the β,β-carotene 15,15'-monooxygenase activity of SEQ ID NO:1 is unpredictable in the art because SEQ ID NO:1 has homology with polypeptides with β,β-carotene 15,15'-dioxygenase activity. These claims amount to a polypeptide with unknown function and a polypeptide with unknown function and unpredictable function has no utility. ***Therefore, there is no specific, substantial, or credible utility*** that is well known, apparent, or implied by the relationship of the instant polynucleotide to the polynucleotide encoding SEQ ID NO:1.

(internal citations omitted) (Paper No. 11, p. 3, lns. 3-15).

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> ***As pointed out by applicants***, the specification supports utility for a β,β-carotene 15,15'-dioxygenase and not for a β,β-carotene 15,15'-monooxygenase. Examples 1-6 all relate to detecting activity, cloning, purification and expression of a β,β-carotene 15,15'-dioxygenase. The specification does not support utility for a β,β-carotene 15,15'-monooxygenase. Identifying a polypeptide as a β,β-carotene 15,15'-monooxygenase does not endow the polypeptide with such a utility.

(Paper No. 14, p. 3, lns. 5-11).

Based on the above citations to the record, it appears the Examiner may have misunderstood Appellants' description of the error in the specification as more than simply misnaming SEQ ID NO:1. (See July 31, 2001 Response, p. 4, lns. 10-12). The Examiner improperly extended Appellants' statements regarding the error to include a misidentified function for the polypeptide sequence set forth in SEQ ID NO:1.

To make the record clear, the ***only*** error in the specification identified by the Appellants is the ***name*** associated with the polypeptide designated as SEQ ID NO:1. The sequences set forth in all the SEQ ID NOs are correct and the Examiner has not even contended, much less demonstrated, that they are not. In fact, all other properties including the polypeptide and polynucleotide sequences, the identified substrate for SEQ ID NO:1 (β-carotene), and the reaction product (retinal) are correctly disclosed in the specification.

Appellants intended to convey to the Examiner that the name of SEQ ID NO:1 was in error – that is all. And, the only consequence of this error in the disclosed name of the enzyme is that the reaction mechanism suggested by the ***name*** is different.[4/] But, a "name" is not claimed, and the substrate, substrate specificity, and reaction product are still correctly identified in the specification for the polypeptide identified as SEQ ID NO:1. (See February 28, 2002 Response, p. 12, ln. 18 – p. 13, ln. 2 and Appendix II).

4/ Moreover, we note that it is axiomatic that an applicant may be his or her own lexicographer. Whether SEQ ID NO:1 is called a "dioxygenase," a "monooxygenase," or a "widget" is irrelevant to patentability, so long as SEQ ID NO:1 is described in the specification in such a manner that one skilled in the art would know how to make and use ***it***.

As is well settled, there is no requirement that an applicant disclose the scientific principle by which a claimed invention works. All that is required is that the specification contain at least one specific, substantial, and credible assertion of utility.

Moreover, even if an applicant misidentifies the scientific principle that explains how the claimed invention works, so long as the specification discloses a utility for the claimed invention and teaches how to make and use the claimed invention (and complies with the other statutory requirements), the disclosure of an erroneous scientific principle is not a bar to patentability. *Cross v. Iizuka*, 224 USPQ 739, 741, nt. 3 (Fed. Cir. 1985) ("... it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 USC §112.").

Based solely on Appellants' disclosure to the PTO, the Examiner summarily concluded that "the claimed invention lacks patentable utility ... [because] the claimed polynucleotides are not supported by either a specific and substantial asserted utility." (Paper No. 11, p. 3, lns. 1-3; and Paper No. 14, p. 3, lns.1-2.).

As is well settled, a specification which contains a disclosure of utility which corresponds in scope to the ***claims must be taken as sufficient to satisfy the utility requirement of §101***, unless there is reason for one skilled in the art to doubt the objective truth of the statement of utility or its scope. *In re Gaubert*, 187 USPQ at 666. The PTO's own guidelines and training materials, which purportedly "do not alter the substantive requirements of 35 USC §§ 101 and 112," recognize the analysis required

to reject claims under these sections. (66 FR at 1098). The analysis requires that the Examiner "[r]eview the claims and the supporting written description" and "determine if the applicant has asserted for the claimed invention ***any*** specific and substantial utility that is credible." (*Id.*). Where, as here, an Examiner concludes that the asserted utility is not specific or substantial, the Examiner "***must***" explain her reasoning, identify the support for her factual findings, and "evaluate ***all*** relevant evidence of record." (*Id.*). The record, however, is devoid of ***any evidence*** that the Examiner considered the specification other than to confirm the disclosure of "dioxygenase activity."

Moreover, in the only discussion of the specification in the Office Actions, the Examiner mischaracterized the examples and created facts without identifying a source. Specifically, the Examiner asserted that "[e]xamples 1-6 all relate to detecting activity, cloning, purification and expression of β,β-carotene 15,15'-dioxygenase." (Paper No. 14, p. 3, lns. 7-8). To one skilled in the art, however, the examples describe how to make, use, and detect a polypeptide having the sequence set forth in SEQ ID NO:1 and its corresponding nucleotide sequence, SEQ ID NO:2. That is what is claimed, not a "name." Notwithstanding the misnaming of the polypeptide sequence (SEQ ID NO:1), the activity assay (Example 1), purification method (Example 2), amino acid sequence analysis (Example 3), cloning process (Example 4), sequence comparison (Example 5), and expression method (Example 6) disclosed in the specification are all true and correspond to the polypeptide and polynucleotide sequences (SEQ ID NOs: 1 and 2) disclosed in the application.

The Examiner, however, summarily dismissed Appellants' showing that the specification contains a disclosure of utility for SEQ ID NO:1 as a participant in the

pathway leading to vitamin A production (*see* July 31, 2001 Response, p. 5, lns. 1-3) by reading into and cobbling together certain statements and raising them to the level of established facts. For example, the Examiner asserted that "[t]he starting material needs to be taught because there are many pathways leading to the production of vitamin A." (Paper No. 11, p. 2, lns. 11-13). This is error. A starting material is disclosed in the specification for the reaction catalyzed by SEQ ID NO:1, namely "*β*-carotene." (*See* Specification, p. 5, lns. 24-25 and Scheme I). Given the disclosure in the specification, one skilled in the art would have recognized that the enzyme disclosed as SEQ ID NO:1 has the function of converting one mole of *β*-carotene into two moles of retinal. The Examiner has not disputed that. Appellants misnaming of SEQ ID NO:1 has no effect on any of the properties disclosed for it in the specification. (*See* July 31, 2001 Response, p. 4, lns. 17-18 and Appendix 2) and the Examiner has provided ***no*** evidence that would suggest otherwise.

The Examiner also asserts that "the *β*,*β*-carotene 15,15'-monooxygenase activity of SEQ ID NO:1 is unpredictable in the art because SEQ ID NO:1 has homology with polypeptides with *β*,*β*-carotene 15,15'-dioxygenase activity." (Paper No. 11, p. 3, lns. 9-11). Again, that is not what is claimed. The Examiner, however, fails to identify on the record what evidence she relies on for this assertion. Without such support, this assertion is nothing more than an unsupported belief. But, a rejection for lack of utility must be based on a factual analysis of the specification and any supporting materials. When such a rejection is not supported by facts, it cannot stand. *See e.g. Raytheon v. Roper*, 220 USPQ 592, 596 (Fed. Cir. 1983) *cert. denied* 469 US 835 (1984) (compliance with §101 is a question of fact) and *In re Oetiker,* 24 USPQ2d at 1444.

Assuming *arguendo* the accuracy of the Examiner's unsupported contention that SEQ ID NO:1 has a homology to β,β-carotene 15,15'-dioxygenase polypeptide sequences, the Examiner must concede that SEQ ID NO:1 has a utility, *e.g.* as a participant in the vitamin A reaction pathway, because β,β-carotene 15,15'-dioxygenases are recognized in the art as enzymes in the vitamin A reaction pathway. (*See e.g.* Specification, p. 6, lns. 3-10 and the documents cited therein). It is well settled that utility may be found for a compound disclosed in a specification, which is described as having a high homology to a known compound with a recognized utility. (*See e.g. In re Jolles*, 206 USPQ 885, 890 (CCPA 1980) and Example 10 of the Revised Interim Utility Guidelines Training Materials entitled "DNA Fragment Encoding a Full Open Reading Frame (ORF), p. 53, ln. 22 – p. 55, ln. 11) (Utility found for a specification disclosing a DNA encoding an ORF. The specification contained no disclosure of the function of the ORF, but disclosed that the ORF had a high level of homology to a DNA ligase.).

The record is further devoid of any evidence that one skilled in this art would doubt the truth of the statements contained in any of Examples 1-6. But that too was the Examiner's burden. Appellants' recognition that the specification merely misnamed SEQ ID NO:1 has ***no*** impact on the sequence disclosed and claimed, its substrate, the substrate specificity, the product produced, or any of the results of the Examples – the only significance attributable to the different names is the precise reaction pathway utilized by the enzyme. (See July 31, 2001 Response, p. 4, lns. 17-18 and Appendix II, p. 2614, col. 2, lns. 6-20 and p. 2615, col. 2, 2nd full paragraph). Again,

the claimed SEQ ID NO operates in accordance with, and is useful as disclosed in the specification. And again, the Examiner has not contended otherwise.

At best, the Examiner, in a single sentence, merely suggested that the Examples cannot be relied on because SEQ ID NO:1 was misnamed in the application. (Paper No. 14, p. 3, Ins. 7-9). The Examiner, however provides no evidence that one skilled in the art would doubt the objective truth of any of the Examples. For example the Examiner provides no evidence that by using the reagents and methods disclosed in Example 4 that one would be unable to make the cDNA shown in Figure 3 (SEQ ID NO:2) or generate the amino acid sequence deduced therefrom set forth in Figure 4 (SEQ ID NO:1).

Because the Examiner misinterpreted the scope of the error in the specification and ignored repeated attempts to clarify the error in the name assigned to the compound of SEQ ID NO:1, she failed to set forth any evidence to support her rejection, failed to explain why one skilled in the art would doubt the object truth of the evidence of utility identified by Appellants, and thereby impermissibly shifted the burden to Appellants to demonstrate a *prima facie* case of utility. This is error and for this reason alone the rejection should be withdrawn.

POINT II

THREE DISCLOSURES OF UTILITY IN THE SPECIFICATION WERE IDENTIFIED – TWO STAND UNREBUTTED - AND THE THIRD WAS DISMISSED BASED ON THE EXAMINER'S FACTUAL ERRORS

Another error in the rejection is that the Examiner responded on the record to only one of the identified assertions of utility contained in the specification, *i.e.* producing vitamin A - from among at least three different utilities identified by Appellants during prosecution. As demonstrated below, the Examiner's sole response was, at best, conclusory and not supported by any facts of record.

In the July 31, 2001 Response, Appellants identified three representative utilities disclosed by the specification for the polypeptide designated by SEQ ID NO:1 (and its corresponding polynucleotide sequence, SEQ ID NO:2) including (1) a participant in the pathway leading to the production of vitamin A; (2) cleavage of carotene molecules; and (3) the production of transgenic plants. (July 31, 2001 Response, p. 5, lns. 1-16):

> It is an object of the present invention to provide a protein having the ***vitamin A producing activity*** of β,β-carotene 15,15'-dioxygenase comprising an amino acid sequence which is identical or homologous to SEQ ID NO:1 (shown in Fig. 4) whereby the degree of homology to SEQ ID NO:1 is at least 60%.

(Specification, p. 7, lns. 15-18).

> The ***carotene can be conveniently cleaved*** enzymatically by ***using a protein of the present invention***.

(Specification, p. 11, lns. 18-19).

> The vector having the gene and the other required genetic structures is then introduced into suitable host cells by well-known methods like transformation, transfection, electroporation or microprojectile bombardment. Depending on the host cell it may be preferred to stably integrate the gene coding for a protein of the present invention into the genome of the host cell. The cells obtained by such methods can then be further propagated and if the cell is a plant cell ***it is possible to generate therefrom transgenic plants***.

(Specification, p. 12, lns. 6-12).

The Examiner never addressed the disclosed utilities of the cleavage of carotene or the production of transgenic plants identified in the July 31, 2001 Response. (*See* p. 5, lns. 7-16 and Paper Nos. 11 and 14). These identified disclosures of utility in the specification stand unrebutted and must be accepted as true. *In re Herrmann*, 120 USPQ 182, 184 (CCPA 1958) (failure of the Examiner and the Board to question factual assertions made by the Appellant "constrained" the CCPA to accept such statements as true.); and MPEP §707.07(f) at 700-98 ("Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of applicants argument and ***answer the substance of it***.").

As demonstrated below, the disclosed utilities of cleaving β-carotene or generating a transgenic plant from a vector "having the gene [*i.e.*, SEQ ID NO:2] and the other required genetic structures" are specific, *i.e.*, "specific to the subject matter claimed;" substantial, *i.e.*, "define a 'real world' use;" and credible, *i.e.*, are "believable to a person of ordinary skill in the art." (*See* Revised Interim Utility Guidelines Training Materials, p. 5, lns. 4-5 and ln. 19 and p. 6, ln. 3).

Claims 6, 10, 11, and 28-32 recite a nucleic acid (or polynucleotide) sequence that encodes SEQ ID NO:1, a vector containing such a nucleic acid sequence, and a host cell transformed with such a vector. Thus, both utilities are specific to the nucleotides (or polynucleotides), vectors, and host cells recited in claims 6, 10, 11, and 28-32. And, the Examiner has provided no evidence to rebut the specificity of the two utilities.

Both utilities - cleaving β-carotene and generating a transgenic plant – define "real world" uses (cleaving β-carotene forms retinal, which is a precursor for vitamin A; and making transgenic plants with SEQ ID NO:1 would be readily recognized as being beneficial for *e.g.*, supplementing animal feeds and bulk manufacturing of the enzyme). And, the Examiner has not even contended otherwise, much less provided evidence to rebut such "real world" uses.

Both asserted utilities would be believable to one of ordinary skill in the art in view of the disclosed structures set forth in SEQ ID NOs:1 and 2, the disclosed substrate (β-carotene), the disclosed reaction product (retinal), and the methods set forth in Examples 1-6. And, the Examiner has not even contended otherwise, much less provided evidence to the contrary.

Because only one utility is needed and because the Examiner has failed to rebut either of these ***two*** disclosed utilities, they must be viewed as true. *In re Herrmann*, 120 USPQ at 184. And, because Appellants have placed unrebutted evidence of utility on the record, the Board should rule that the utility provision of §101 has been met, and should reverse the rejection for this reason also.

Moreover, with respect to the third disclosed utility of having "vitamin A producing activity," the Examiner summarily concluded (1) that the starting material needs to be taught; and (2) that the cleavage of β,β-carotene with β,β-carotene 15,15'-monooxygenase will have a different result than the production of two moles of retinal as disclosed in the specification:

> ***The starting material needs to be taught*** because there are many pathways leading to the production of vitamin A without any teachings on the substrate specificity. The specification teaches that of β-carotene by β,β-carotene 15,15'-dioxygenase results in two moles of retinal. ***This reaction will have different results*** with a polypeptide having the current identification, β,β-carotene 15,15'-monooxygenase activity.

(Paper No. 11, p. 2, lns. 9-16).

The Examiner's assertion that "the starting material needs to be taught" simply misses the point and misapprehends the standard for compliance with §101. Appellants identified a utility for the currently claimed subject matter, namely, that the isolated polynucleotide encodes a polypeptide of SEQ ID NO:1, which is "a protein having the vitamin A producing activity of β,β-carotene 15,15'-dioxygenase." (Specification, p. 7, lns. 15-18 and July 31, 2001 Response, p. 5, lns. 1-6). This assertion, under the PTO's own rules and precedent, is presumed to be sufficient to comply with the §101 requirements of utility unless one skilled in the art would have reason to question the truth of Appellants' statements. *In re Gaubert*, 187 USPQ at 666 *citing In re Langer*, 183 USPQ 288, 297 (CCPA 1974). ("As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented ***must*** be taken as sufficient to satisfy

the utility requirement of §101 for the entire claimed subject matter ***unless*** there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.").

In the rejection, the Examiner provided no evidence that one skilled in the art would question the objective truth that the claimed SEQ ID NO:1 has the utility of encoding "a protein having the vitamin A producing activity of β,β-carotene 15,15'-dioxygenase." The specification clearly describes SEQ ID NO:1 as having the "vitamin A producing activity of β,β-carotene 15,15'-dioxygenase." (Specification, p. 7, lns. 15-17). This disclosure does not say that the "invention" is limited to β,β-carotene 15,15'-dioxygenase – only that it "***provide a protein having***" the vitamin A producing activity of the dioxygenase enzyme, *i.e.*, the ability to form retinal from β-carotene. Thus, the specification's disclosure is broad enough to embrace proteins, such as SEQ ID NO:1 that have an activity of forming retinal from β-carotene.

In addition, the Examiner also did not provide any evidence that would lead one to believe that the polypeptide whose amino acid sequence is set forth in SEQ ID NO:1 could not use β-carotene as a substrate. Nor did the Examiner provide any evidence that would lead one to believe that the polypeptide defined by the amino acid sequence set forth in SEQ ID NO:1 would not produce two moles of retinal from β-carotene. But that was the kind of evidence required to demonstrate that one would question the truth of the disclosure that the polypeptide defined by the amino acid sequence set forth in SEQ ID NO:1 has the ***vitamin A producing activity*** of β,β-carotene 15,15'-dioxygenase (not that it is β,β-carotene 15,15'-dioxygenase). Because the Examiner failed to provide any evidence to support her conclusory statements, she

failed to meet her burden of setting forth a *prima facie* case, and the rejection should be reversed for this reason also.

Moreover, the lack of evidence in the rejection is understandable because the rejection is predicated on erroneous assumptions by the Examiner. The first error in the Examiner's argument is that "the starting material is not taught." That is wrong, it clearly is. (*See e.g.* Specification, p. 5, lns. 18-20 and Scheme 1) ("The enzyme is located in the cytosol and ***forms retinal from β-carotene, as the principal substrate***, in the presence of oxygen according to Scheme 1....").

The second error in the Examiner's argument is the contention that a monooxygenase "will have different results" compared to a dioxygenase in the disclosed reaction. Apart from the fact that the Examiner did not present evidence that it would, as set forth above, the reaction disclosed in the specification forms "retinal from β-carotene." (*Id.*). Thus, there is no change in the substrate that is utilized in the reaction disclosed in the specification. There is no change in the product produced in the reaction disclosed in the specification. And, there is no change in the enzyme, *i.e.*, the polypeptide whose amino acid sequence is set forth in SEQ ID NO:1, used in the reaction disclosed in the specification. (*See e.g. Id.*; and Appendix II, p. 2613 and 2616, which demonstrates that a "monooxygenase" uses the ***same*** substrate and forms the ***same*** product as the enzyme named "dioxygenase" in the specification but has a different reaction pathway. That pathway is ***not*** claimed.).

Accordingly, because the Examiner's sole basis for rejecting Appellants' identification of producing vitamin A as a utility for the claimed invention has been demonstrated to be premised on facts that are wrong, the asserted utility of producing

vitamin A also stands unrebutted and must be accepted as true. *In re Herrmann*, 120 USPQ at 184. Moreover, when a rejection based on §101 is predicated on erroneous facts, it cannot stand, and must be reversed. *Ex parte Morizane*, 2001 WL 1922409, *1 -*2 (B.P.A.I. 2001) ("The Examiner argues that the appellant's claimed method cannot work because glass cannot be vitrified at temperatures as low as 200°C or below ... The Examiner has provided no evidence that if the appellant's claimed method rather than Kondo's sol-gel method is used, metal oxide micro-spherules cannot be formed at a temperature of 200°C or below. Consequently, we are not persuaded by the examiner's argument that the appellant's claimed method lacks utility."); *Ex parte Porter*, 25 USPQ 1144, 1447 (B.P.A.I. 1992) (reversing an examiner's §112, first paragraph rejection because based on factual inaccuracies). For this reason also, the rejection should be reversed.

POINT III

THE EXAMINER FAILED TO CONSIDER THE SPECIFICATION AS WHOLE, AND COMPLETELY IGNORED ADDITIONAL DISCLOSURES OF UTILITY IN THE SPECIFICATION IDENTIFIED BY APPELLANTS

To support a claim for a patent, an applicant need only demonstrate a ***single utility for one purpose*** – notwithstanding that that the applicant may have additional statements of utility for a different purpose. So long as there is at least one disclosure of utility sufficient to meet the statutory requirements under §101, the application ***cannot*** be rejected for lack of utility. At most, the Examiner may require that the specification be amended to cancel incredible or misleading assertions. *Ex parte Lanham*, 121 USPQ 223, 225 (B.P.A.I. 1958) ("***In order to sustain a pat nt it is only***

n cessary that a single utility be disclos d. In this case we see no objection to retaining references to the other proposed uses unless they are incredible or misleading."); *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 598 (Fed Cir. 1983) (citing Treatise: "When a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown."); and *Standard Oil Co. v. Montedison S.p.A.*, 212 USPQ 327, 344 (3rd Cir. 1981) ("Proof of one of the disclosed utilities suffices to meet the statutory utility requirement.").

Appellants identified for the Examiner in the July 31, 2001 and February 28, 2002 Responses, where in the specification there could be found assertions of utility independent from the name assigned to the polypeptide represented by SEQ ID NO:1. (July 31, 2001 Response, p. 5, lns. 1-16 and February 28, 2002 Response, p. 7, ln. 7 – p. 11, ln. 3). For example, as identified explicitly in the February 28, 2002 Response, the specification includes the following assertions of utility:

> ***A process is also provided for the production of vitamin A.*** This process includes enzymatically cleaving β-carotene by a polypeptide as described above. (p. 2, lines 21-22).
>
> Figure 8 is a chromatogram demonstrating that the peak from Fig. 7 representing ***the only product of the enzymatic cleaving is retinal.*** (p. 5, lines 8-9).
>
> ***The nucleic acid sequences of the present invention code for a protein of the present invention*** or a part thereof. (p. 9, lines 7-8).
>
> ***The nucleic acid sequences of the present invention can be used as antisense RNA probes*** for *in situ* hybridization. (*Id.* at lines 16-17).

Another diagnostic option is ***quantification of mRNA by RT-PCR***. (p. 10, line 11).

Since the protein has been expressed and a method for purifying the protein is described in detail in the examples ***the person skilled in the art can use the protein or peptides derived from the amino acid sequences in order to generate antibodies which specifically react with the protein***. (*Id.* at lines 15-18).

The antibodies can also be used in laboratory methods like Western blots or immuno-precipitations. Preferably such antibodies can be used in immunohistochemistry to detect epitopes of β,β-carotene 15,15'-dioxygenase in embedded or fixed tissues or cells of any species of interest. (p. 11, lines 6-9).

A preferred source of β-carotene is the alga *Dunaliella bardawil* which has a high endogenous level of β-carotene. Suitable algae can be grown conveniently and β-carotene can be purified therefrom at rather low cost. ***The carotene can be conveniently cleaved enzymatically using a protein of the present invention***. (p. 11, lines 15-20).

The vector having the gene and the other required genetic structures is then introduced into suitable host cells by well-known methods like transformation, transfection, electroporation or microprojectile bombardment. ***Depending on the host cell it may be preferred to stably integrate the gene coding for a protein of the present invention into the genome of the host cell. The cells obtained by such methods can then be further propagated and if the cell is a plant cell it is possible to generate therefrom transgenic plants***. (p. 12, lines 6-12).

D) Activity screening of the chicken cDNA library:

90 of the above pools were tested for activity in a transactivation assay based on the detection of retinoic acid which is produced in eukaryotic cells after β-carotene cleavage. The principle of the activity test is shown in Fig. 2. (p. 21, lns. 23 - 27).

* * *

> The obtained cDNA sequence is shown in Figure 3 and the amino acid sequence deduced therefrom in Figure 4.
>
> Figure 4 shows the derived amino acid sequence having 526 residues.
>
> (p. 22, lns. 25 - 28).
>
> After expression in *E. coli* and purification over a metal chelate column, ***the protein shows cleavage activity with β-carotene as substrate***. Retinal was the only product detected by HPLC after incubation with β-carotene. No apocarotenals or other metabolites were found. This was proved by HPLC analysis as shown in Figs. 7 and 8.
>
> (p. 25, lines 9-12).

To summarize the disclosure cited above, the specification contains the following additional assertions of utility:

1. the nucleic acid sequences can be used as RNA probes;
2. diagnostic tests based on quantification of mRNA by RT-PCR;
3. generation of antibodies; and
4. generation of transgenic plants.

When these additional assertions of utility were identified for the Examiner, she summarily dismissed them in one sentence: "Applicants arguments filed on March 11, 2002 have been fully considered but they are not persuasive." (Paper No. 14, p. 2, lns. 16-17).

Again, the Examiner's sole basis of rejection is that SEQ ID NO:1 was misnamed in the specification: "Identifying a polypeptide as a β,β-carotene 15,15'

monooxygenase does not endow the polypeptide with such a utility." (Paper No. 14, p. 3, lns. 10-11). Whether or not the disclosure of the complete structure of a polypeptide also requires that a name indicative of the polypeptide's reaction mechanism be provided in order to comply with the utility requirement does not relieve the Examiner of her duty to consider other additional disclosures of utility in the specification.

In the February 28, 2002 Response, at least four additional assertions of utility disclosed in the specification were identified by Appellants. For whatever reason, the Examiner chose to ignore these proffers. Accordingly, under binding precedent and the PTO's own rules, these assertions of utility must be taken as true. *In re Herrmann*, 120 USPQ at 184, MPEP §2107.02 III.A. at 2100-39 ("Thus, *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true.").

Because the Examiner failed to consider additional disclosures of utility for the presently claimed invention – disclosures that were repeatedly identified for her – and failed to present any evidence that one of ordinary skill in the art would doubt the truth of such statements, the rejection should be reversed. *Id.*; *see also In re Oetiker*, 24 USPQ2d at 1444.

POINT IV

THE PRIMER/PROBE/TEST KIT CLAIMS (CLAIMS 12-15 AND 34-36) AND THE METHOD CLAIMS (CLAIMS 19-27) ARE SEPARATELY PATENTABLE IN VIEW OF SPECIFIC DISCLOSURES IN THE SPECIFICATION IGNORED BY THE EXAMINER

A. Claims 12-15 and 34-36

The evidence of record clearly shows that Examiner treated all the claims as standing and falling together even though the claims were of different scope including claims directed to isolated nucleotides or polynucleotides (claims 6, 10, 11, 28-30), primers (claims 12, 34, and 35), a probe (claim 13), test kits (claims 14, 15, and 36), methods (claims 19-26), host cells (claims 26, 27, and 32), and vectors (claim 31).

An additional error in the rejection was the failure of the Examiner to consider the primer/probe/test kit claims, namely claims 12-15 and 34-36, separate from the rest of the claims on appeal. Claims 12-15 and 34-36 are self-contained claims that recite their own utilities, which utilities were completely ignored by the Examiner.

For example, claims 12, 34, and 35 (the "primer claims") are directed to various "primers" used for amplifying a gene or a polynucleotide coding for the polypeptide of SEQ ID NO:1. There is no evidence of record that the Examiner considered a primer for SEQ ID NO:1 separately from SEQ ID NO:1. Yet, a polynucleotide sequence that is useful for amplifying SEQ ID NO:1, whatever name may be assigned to SEQ ID NO:1, is inherently useful in test kits or assays for detecting and/or amplifying the gene or a fragment thereof (*see e.g.* claims 14, 15, and 36).

It is fundamental that only a minimal degree of utility is required to satisfy § 101:

> ***the fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility***. *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 598 (Fed. Cir. 1983); *Carpet Seaming Tape Licensing Corp. v. Best Seam, Inc.*, 216 USPQ 873, 880 (9th Cir. 1982). ***Some degree of utility is sufficient for patentability***. *E.I. duPont de Nemours & Co. v. Berkley and Co.*, 205 USPQ 1, 10 *fn.*17 (8th Cir. 1980).

Envirotech Corp. v. Al George Inc., 221 USPQ 473, 480 (Fed. Cir. 1984)

Similarly, the MPEP also explains in § 2107.01 (II):

> "[t]o violate [35 U.S.C.] 101 the claimed device must be ***totally incapable of achieving a useful result.***" *Brooktree Corp. v. Advanced Micro Devices, Inc.,* 24 USPQ 2d 1401, 1412 (Fed. Cir. 1992) (emphasis added). *See also, E.I. duPont De Nemours and Co. v. Berkley and Co.,* 205 USPQ 1, 10 n.17 (8th Cir. 1980) ("A small degree of utility is sufficient... The claimed invention must only be capable of performing some beneficial function... An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required...Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility.... In short, the defense of non-utility cannot be sustained without proof of total incapacity." If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based as a whole based on a lack of utility is not appropriate. *See In re Brana*, 34 USPQ2d 1435 (Fed. Cir. 1995); *In re Gardner,* 177 USPQ 396 (CCPA), *reh'g denied*, 480 F.2d 879 (CCPA 1973); *In re Marzocchi,* 169 USPQ 367 (CCPA 1971). [Underline original].

In view of the well recognized low threshold for compliance with the utility requirement, it is respectfully submitted that the claims directed to primers, probes, and test kits recite sufficiently specific, substantial, and credible uses that they comply with the requirement of §101. Furthermore, because there is a complete lack of evidence that the Examiner even considered claims 12-15 and 34-36 and their separate recitations of utility ("primer," "probe," and "test kit") from the nucleotide or

polynucleotide claims, the Examiner failed to meet her burden of setting forth a *prima facie* case of non-utility.

B. Claims 19-27

Claims 19-25 are directed to a "method of introducing a cDNA coding for a polypeptide of SEQ ID NO:1 into a host cell" and claims 26 and 27 are directed to host cells made according to the method recited in, *e.g.*, claim 19. Such methods include methods for making transgenic plants. (*See e.g.* claim 20). As noted above in Point II, the Examiner failed to consider the utility specifically recited in the claims of making transgenic organisms, *e.g.*, a transgenic plant as recited in claim 20, let alone the added disclosure of making transgenic organisms, including transgenic plants in the specification. (*See* Specification, p. 12, lns. 6-12).

There is no evidence that the Examiner considered and rejected the method claims as not reciting or being supported by a sufficiently specific utility in the specification. There is no evidence that the Examiner considered and rejected the method claims as not reciting or being supported by a sufficiently substantial utility in the specification. And, there is no evidence that the Examiner considered and rejected the method claims as not reciting or being supported by a sufficiently credible utility in the specification. Thus, the utility recited in the method claims and further disclosed in the specification stands unrebutted, and must be accepted as true. *In re Herrmann*, 120 USPQ at 184. Accordingly, the Examiner did not meet her burden of setting forth a *prima facie* case of lack of utility for claims 19-27.

For all of these reasons, the rejection of claims 12-15, 34-36, and 19-27 should be reversed.

POINT V

THE EXAMINER'S ENABLEMENT REJECTION DOES NOT REST ON ANY BASIS INDEPENDENT OF THE UTILITY REJECTION AND MUST FAIL FOR THE SAME REASONS AS THE UTILITY REJECTION

The rejection of claims 6-36 under 35 USC §112, first paragraph for lack of enabling disclosure is based solely on the Examiner's conclusion that the claims are not supported by either a specific utility or a well established utility so that one "would not know how to use the claimed invention so that it would operate as intended without undue experimentation." (Paper No. 11, p. 4, lns. 1-4; and Paper No. 14, p. 3, lns. 17-21).

As is well settled, the "how to use" prong of §112, first paragraph incorporates as a matter of law the requirement of §101 that the specification disclose as a matter of fact a utility for the claimed invention. *In re Watson*, 186 USPQ 11, 17 (CCPA 1975) (reversing a §112, first paragraph rejection because the §101 rejection was also reversed); *See also In re Ziegler*, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993). Accordingly, when a rejection under §101 is shown to be factually deficient, a corresponding rejection under the "how to use" prong of §112, first paragraph must be withdrawn as a matter of law. *Ex parte Morizane*, 2001 WL 1922409, *2 (B.P.A.I. 2001) ("In the rejection under 35 U.S.C. §112, first paragraph, enablement requirement, the examiner relies upon the same rationale used in the rejection under 35 USC §101. We are not convinced by the examiner's argument for the reasons set forth above regarding that rejection. For the above reasons, we conclude that the examiner has not carried the burden of establishing a *prima facie* case of lack of utility or of nonenablement.

Accordingly, we reverse ...."); and MPEP §2107.01 IV at p. 2100-36 ("A 35 U.S.C. §112, first paragraph rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. §101. In other words, Office personnel should ***not*** impose a 35 U.S.C. §112 first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper. In particular, the factual showing needed to impose a rejection under 35 U.S.C. §101 must be provided if a rejection under 35 U.S.C. § 112, first paragraph, is to be imposed on 'lack of utility' grounds.")

For at least the reasons set forth above in Points I-IV, the Examiner failed to set forth a *prima facie* case of lack of utility. Because the Examiner has failed to meet her burden with respect to the utility rejection, as a matter of law, the rejection under §112, first paragraph must also fail. For this reason the rejection based on §112, first paragraph should be reversed.

CONCLUSION

For all of the foregoing reasons, it respectfully is submitted that the Examiner has failed to make out a *prima facie* case of lack of utility and non-enablement and hence the rejection of claims 6, 10-15, 19-32, and 34-36 should be reversed.

Respectfully submitted,

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APPENDIX I

6. An isolated nucleic acid sequence encoding a polypeptide of SEQ ID NO:1.

10. An isolated nucleic acid sequence according to claim 6 wherein the nucleic acid is a deoxyribonucleic acid.

11. An isolated nucleic acid sequence comprising an antisense ribonucleic acid, which binds to the nucleic acid sequence according to claim 6.

12. A primer for amplifying a gene coding for the polypeptide of SEQ ID NO:1 which primer comprises a fragment of the nucleic acid sequence according to claim 6.

13. A probe for detecting a gene coding for the polypeptide of SEQ ID NO:1 which probe comprises a fragment of the nucleic acid sequence according to claim 6.

14. A test kit for amplifying and/or detecting a gene or a fragment thereof coding for the polypeptide of SEQ ID NO:1 wherein the test kit comprises at least one primer according to claim 12.

15. A test kit for amplifying and/or detecting a gene or a fragment thereof coding for the polypeptide of SEQ ID NO:1 wherein the test kit comprises at least one probe according to claim 13.

19. A method for introducing a cDNA coding for the polypeptide of SEQ ID NO:1 into a host cell comprising introducing a cDNA coding for the polypeptide of SEQ ID NO:1 into a vector suitable for the host cell and introducing the vector into the host cell.

20. A method according to claim 19 wherein the host cell is a plant cell.

21. A method according to claim 19 wherein the host cell is a prokaryotic cell.

22. A method according to claim 19 wherein the host cell is a yeast cell or a fungal cell.

23. A method according to claim 19 wherein the host cell is an alga cell.

24. A method according to claim 19 wherein the host cell is a mammalian cell.

25. A method according to claim 24 wherein the mammalian cell is a human cell.

26. A host cell obtained by the method of claim 19.

27. A host cell according to claim 26 which comprises a cDNA coding for the polypeptide of SEQ ID NO:1 obtained from another species.

28. An isolated polynucleotide which encodes the polypeptide of SEQ ID NO: 1 comprising SEQ ID NO:2.

29. An isolated polynucleotide according to claim 28 which consists essentially of SEQ ID NO: 2.

30. An isolated polynucleotide according to claim 28 which consists of SEQ ID NO: 2.

31. A vector comprising the polynucleotide of SEQ ID NO: 2.

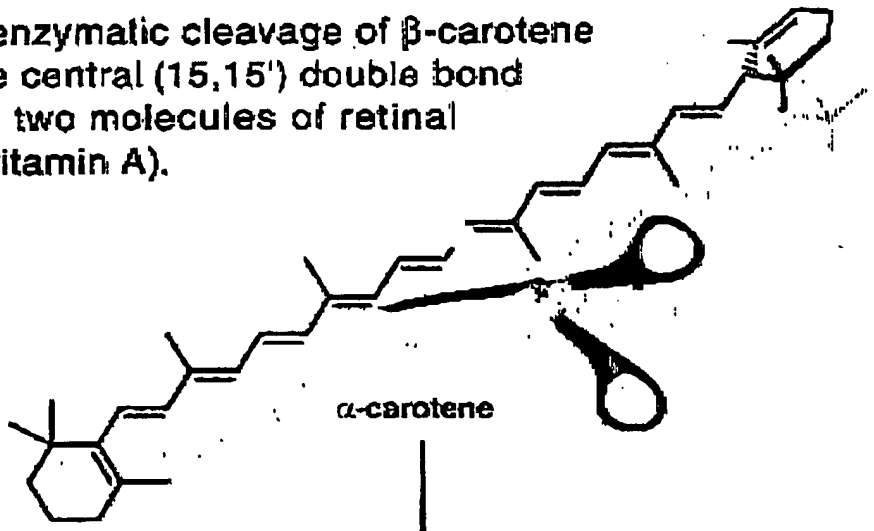
32. A host cell transformed with the vector of claim 31.

34. A primer set for amplifying a polynucleotide encoding the polypeptide of SEQ ID NO:1 comprising SEQ ID NO:8 as a 5' primer and SEQ ID NO: 9 as a 3' primer.

35. A primer set for amplifying a polynucleotide encoding the polypeptide of SEQ ID NO:1 comprising a polyT/Not reverse primer and SEQ ID NO:10 as a forward primer.

36. A kit for amplifying and/or detecting a polypeptide or fragment thereof encoding the polypeptide of SEQ ID NO:1 comprising at least one primer selected from the group consisting of SEQ ID NOs:8, 9, and 10.

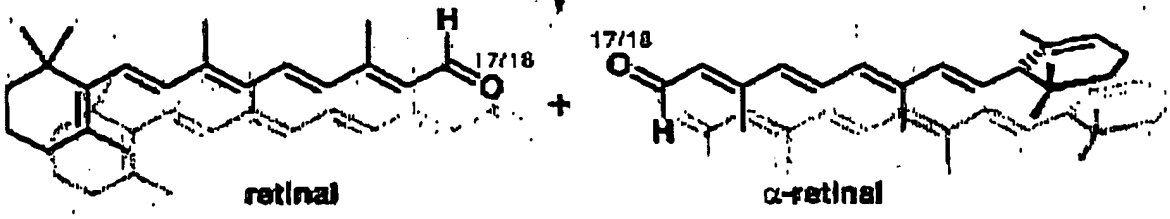
The enzymatic cleavage of β-carotene at the central (15,15') double bond gives two molecules of retinal (provitamin A).



α-carotene

60.3 kDa protein from chicken intestinal mucosa

$^{17}O_2$ $H_2{}^{18}O$



retinal α-retinal

Investigation of the reaction mechanism with α-carotene as a substrate revealed a monooxygenase pathway since both $^{17}O_2$ and $H_2{}^{18}O$ are incorporated into the metabolites.

Find out more on the following pages.

The Reacti n Mechanism of the Enzyme-Catalyzed Central Cleavage f β-Carotene to Retinal**

Michele G. Leuenberger, Caroline Engeloch-Jarret, and Wolf-D. Woggon*

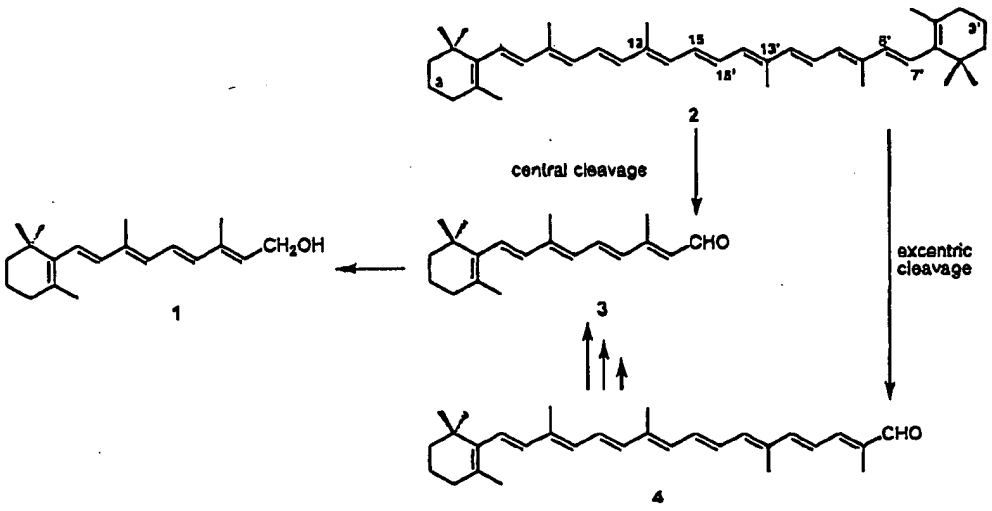
Dedicated to Professor Synnøve Liaaen-Jensen

Although it has been known since 1930 that vitamin A or retinol (**1**) derives in vivo from β-carotene (**2**),[1] the enzymatic origin of β-carotene cleavage was only shown in 1965 when Olson and Hayaishi reported the identification of in vitro activity of an enzyme from rat liver and rat intestine. This enzyme catalyzes the central cleavage of **2** to retinal (β-retinal, **3**; Scheme 1).[2] Later an alternative, probably less significant, pathway was discovered involving excentric cleavage of **2** to yield apo-carotenals such as **4**, which are subsequently degraded to **3**.[3]

During the last 35 years many groups have tried unsuccessfully to purify the enzyme catalyzing the central cleavage of β-carotene **2**,[4] and quite a number of mechanistic investigations have been published which involved crude enzyme preparations or in vivo experiments.[2, 5, 6] Solid information, however, could only be obtained for two aspects of the problem: The enzyme requires molecular oxygen, and the central cleavage proceeds stoichiometrically to yield approximately two moles of retinal from one mole of β-carotene.[7] Most of the other experiments regarding the incorporation of oxygen from water and concerning the metal involved in catalysis can be valued as inadequate.[8] Nevertheless the enzyme that catalyzes the central cleavage of **2** was termed β-carotene 15,15'-dioxygenase (EC1.13.11.21) and often the enzyme was believed to be an iron dioxygenase.[2, 9]

Recently we[10a] and others[10b] have been able for the first time to identify the protein which catalyzes the central cleavage. We have developed a purification protocol for the enzyme from chicken intestinal mucosa and it has become possible to overexpress the functional 60.3 kDa protein in BHK (baby hamster kidney) cells.[10a,c] We have also investigated the substrate specificity of the enzyme with the aim of identifying a nonsymmetrical carotenoid that could be utilized for investigation of the mechanism.[11] This aspect was mainly overlooked in earlier work, we believe. However, only the use of a nonsymmetrical carotenoid as a substrate to yield different aldehydes can provide exact information on the incorporation of oxygen from water and/or air into cleavage products and, hence, distinguish a monooxygenase from a dioxygenase mechanism.

Substrate specificity studies revealed three nonsymmetrical carotenoids, **5**–**7**, that are readily cleaved by the enzyme (40–50% of the yield obtained for **2** under standard conditions) to furnish the corresponding aldehydes, for example, **5**→**3** and **8** (Scheme 2). α-Carotene **5** was chosen as the best candidate because it was available in isomerically pure form, and it was expected that aldehydes **3** and **8** would behave similarly in the subsequent reactions that would be required for mass spectrometry (MS) analysis of the distribution of the labeled oxygen in both cleavage products. In this context it is important to note that aldehydes such as **3** and **8** are not directly suitable for isotopic analysis of an oxygen label in the carbonyl group[12] because this label easily exchanges with the medium at the pH value of incubation (pH 7.8).[13] Thus, we decided for a combined enzyme assay with addition of horse liver alcohol dehydrogenase (HLADH) to reduce **3** and **8** in situ to the corresponding alcohols retinol (**1**) and α-retinol (**9**). Alcohols **1** and **9** are also unsuitable for tandem gas chromatography/mass spectrometry (GC-MS) analysis because both eliminate water. Thus, after quenching of the incubation and high-pressure liquid chromatography (HPLC) purification of alcohols **1** and **9** (Figure 1a), derivatization to the silyl ethers **10** and **11** was required (Figure 1b).



Scheme 1. Enzymatic cleavage of β-carotene **2**. Routes to the formation of retinol **1**.

Control experiments revealed that the rates of reduction of **3** and **8** are the same. Exchange of the carbonyl oxygen of **3** with the buffer medium was investigated under conditions similar to the incubation conditions, that is, **3** was added to a

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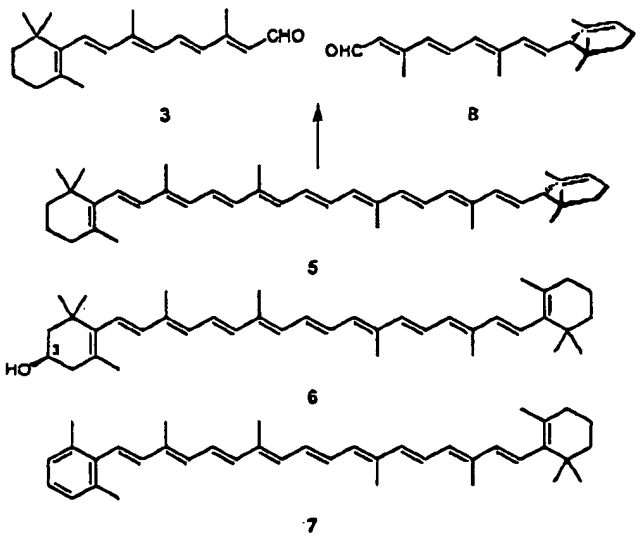


Scheme 2. Nonsymmetrical substrate analogues of the enzyme that catalyzes the central cleavage of 2. Cleavage of α-carotene 5 to form the aldehydes 3 and 8.

solution of HLADH in $H_2{}^{18}O$ as slowly as it would be produced by enzymatic cleavage of 5 (3.5 nmol h^{-1}). According to MS analysis of the retinyl silylether 10, exchange of the ^{18}O label between 3 and $H_2{}^{18}O$ is <5%.

For the decisive incubation experiment with 5 the native enzyme was employed due to its favorable turnover, which is ≈2.5 times higher than the hexahistidine-tailed protein overexpressed in BHK cells. Highly enriched oxygen sources, such as 85% $^{17}O_2$ and 95% $H_2{}^{18}O$, were used. GC-MS analysis of the silylethers 10 and 11 with the focus on the molecular ion

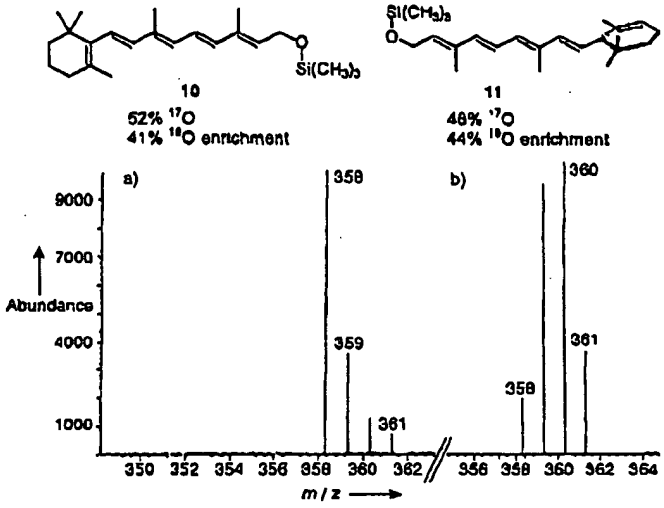


Figure 2. Mass spectra: a) silylether 10 with natural abundance of oxygen isotopes; b) $^{17}O/^{18}O$-enriched 10 from incubation of 5 in the presence of $^{17}O_2$ and $H_2{}^{18}O$.

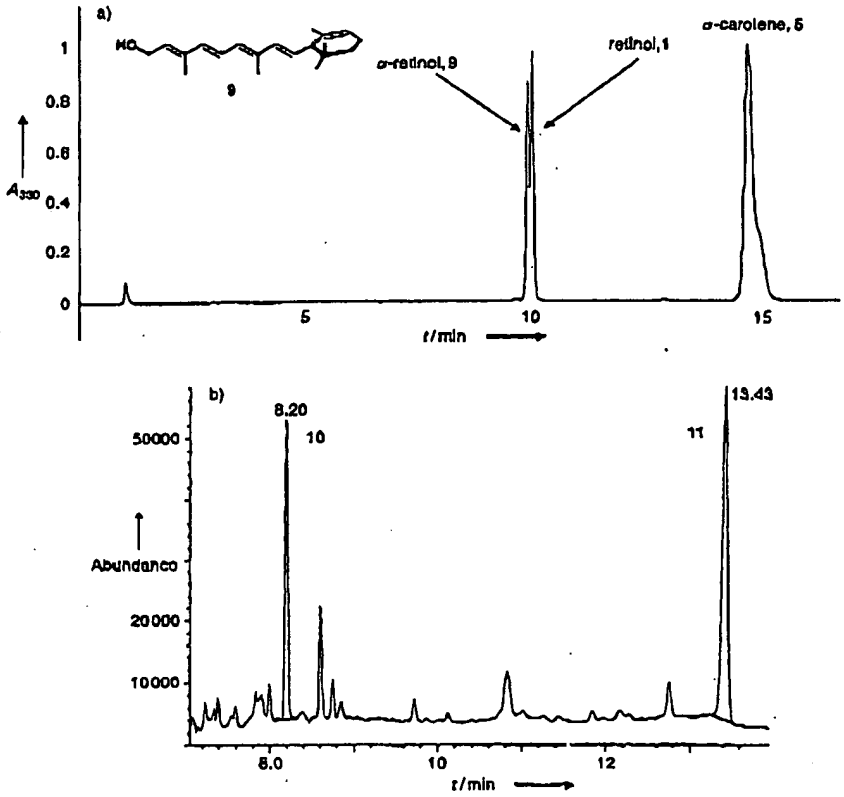


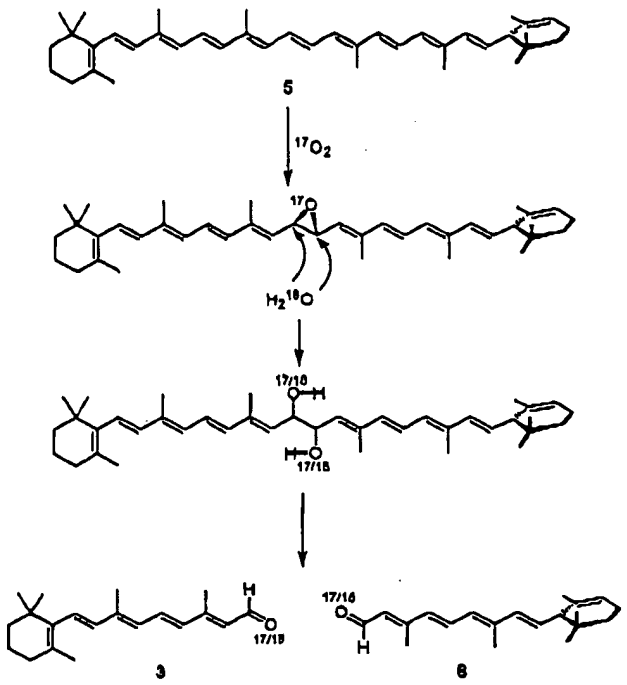
Figure 1. a) HPLC trace recorded after incubation of α-carotene 5; b) GC trace for 10 and 11, the silylethers of the metabolites of 5.

area revealed, within experimental error, equal enrichment of the ^{17}O and ^{18}O label in both derivatives of metabolites 3 and 8 (Figure 2). This result proves for the first time the incorporation of one ^{17}O atom of molecular oxygen and the concomitant incorporation of one ^{18}O atom from labeled water.

Accordingly, and in contrast to earlier beliefs, the reaction mechanism of enzymatic central β-carotene cleavage is not in agreement with a dioxygenase-catalyzed procedure. A dioxygenase mechanism ([2+2] cycloaddition to the central C15—C15′ doubl bond, followed by fragmentation of the intermediate dioxetane) would require the incorporation of one complete oxygen molecule into the product aldehydes and the absence of any ^{18}O label originating from the labeled water.

Experimental evidence provided here accounts for a monooxygenase-type mechanism, as shown in Scheme 3, in which the first step is an epoxidation of the central double bond of 5. This is followed by unselective ring opening with water and final diol cleavage to yield the aldehydes 3 and 8.

Another small experimental detail agrees with the m nooxygenase mechanism. Given the enrichment of the labels in both oxygen



Scheme 3. The reaction mechanism of the central cleavage of α-carotene 5 catalyzed by the 60.3 kDa cytosolic monooxygenase purified from chicken's intestinal mucosa. The mechanism for β-carotene 2 is thought to be analogous.

sources, one would expect, in case of quantitative O-incorporation, the following isotopic enrichments for **10** and **11**: 10% ^{16}O, 42.5% ^{17}O, and 47.5% ^{18}O. Experimentally, however, one finds 5–8% higher ^{17}O enrichment than calculated along with the correspondingly lower ^{18}O enrichment (systematic deviation $\leq \pm 2\%$). This difference can be explained by assuming that ^{17}O-labeled water originating from $^{17}O_2$ cleavage in the active site "dilutes" the $H_2{}^{18}O$ oxygen source in situ.

The nature of the metal complex involved in O_2 cleavage and epoxidation still has to be elucidated. At present it is only certain that this first step of carotene metabolism is not a P450-catalyzed reaction because the heme-thiolate chromophore ($\lambda_{max} \sim 415$ nm) is absent in the purified protein (broad absorption without fine structure between 200–280 nm) as well as in the overexpressed enzyme. Interestingly the monooxygenase mechanism resembles, at least in part (the epoxidation), the mechanism we previously proposed for a supramolecular enzyme model catalyzing the regioselective cleavage of **2** and **7**.[14]

Experimental Section

Enzymatic reaction conditions: α-carotene **5** ((6′*R*)-β,ε-carotene) was obtained from F. Hoffmann-La Roche (Basel) and stored at −18 °C. A stock solution of **5** in benzene (10 mM) was freshly prepared. In a glass vial the stock solution of **5** (40 μL), α-tocopherol solution (50 μL, 43 mg mL^{-1} in hexane), and tween 40 solution (200 μL, 400 μL in 10 mL acetone) were evaporated with a gentle stream of N_2 in a heated block (45 °C). Tricine buffer ($H_2{}^{18}O > 95\%$; 1 mL, 150 mM; pH 7.8, 45 °C) was added and the solution was gently mixed until almost complete solubilization. The substrate solution was added to a 25-mL flask containing tricine buffer ($H_2{}^{18}O > 95\%$; 3.5 mL, 150 mM; pH 7.8), glutathione (12 mg), sodium cholate (1 mg), and nicotinamide adenine dinucleotide, reduced form (NADH; 50 mg). The mixture was cooled to −180 °C while connected to a high-vacuum line (3×10^{-2} mbar) and then degassed three times. Finally labeled molecular oxygen (> 85% $^{17}O_2$; 20 mL; 2.15 bar) was condensed on the surface of the frozen solution (−180 °C). The mixture was allowed to warm up, and after reaching 25 °C the system was allowed to equilibrate over 30 min. In a separate flask the enzyme purified by hydrophobic interaction chromatography (HIC)[14] (from ≈ 10 g mucosa of one chicken's duodenum) was dissolved in tricine buffer ($H_2{}^{18}O > 95\%$; 500 μL, 150 mM; pH 7.8). HLADH (80 μL, 11.1 mg mL^{-1}, 2.9 U mg^{-1} protein; Fluka AG, Buchs) was added. Argon was passed through the solution for 30 min/25 °C to remove $^{16}O_2$. The enzymatic reaction was started by adding this solution to the substrate solution (final concentration of **5**: 80 μM). After incubation for 7.5 h at 37 °C in the dark, the reaction was quenched by addition of acetonitrile (4 mL). The mixture was extracted three times with chloroform (4 mL) and the collected organic phases were evaporated to dryness.

Purification by HPLC: The residue obtained as described above was separated by analytical HPLC (LiChrospher 100 RP-18 5 μm, dimensions: 125 × 4.6 mm, 25 °C, flow rate: 1 mL min^{-1}, eluents and gradients: 100% solution of acetonitrile/1% NH_4OAc_{aq} (1:1) → 100% solution of acetonitrile/*i*PrOH (1:1) over 10 min, the eluent remained the same for 5 min, then → 100% solution of acetonitrile/1% NH_4OAc_{aq} (1:1) over 2 min; diode array detector at 330 nm for **1** (R_t = 10.0 min) and **9** (R_t = 9.9 min), and 455 nm for **5** (R_t = 14.9 min). The mixture of retinoids was collected, evaporated, and concentrated in a 100-μL vial.

Silylation and GC-MS analysis: The mixture of the two products **1** and **9** was dissolved in hexane (5 μL). A syringe was purged several times with *N,O*-bis(trimethylsilyl)acetamide and then directly used to take an aliquot (1 μL) of the solution of **1** and **9**. Thus, silylation occurred in the syringe followed by immediate splitless injection (285 °C) into the GC column (cross-linked 5% phenylmethyl silicone, dimensions: 25 m × 0.2 mm, film thickness: 0.33 μm, 30 s purge delay; temperature program: 150 °C → 250 °C at 25 °C min^{-1} and then constant at 250 °C).[10] Selected ion monitoring analysis (electron ionization, 70 eV) was pursued for the $[M^+]$ regions of the spectra for **10** (R_t = 8.2 min) and **11** (R_t = 13.4 min). The retention times of the retinoids **1** and **9** on HPLC and of the silyl derivatives **10** and **11** on GC were confirmed by injection of authentic material.

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Saddle-Shaped Six-Coordinate Iron(III) Porphyrin Complexes Showing a Novel Spin Crossover between $S = 1/2$ and $S = 3/2$ Spin States**

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Spin states of iron(III) porphyrins are controlled by the number and nature of axial ligands.[1] The coordination of nitrogen bases such as imidazole (HIm) and pyridine results in the formation of low-spin ($S = 1/2$) six-coordinate complexes. In contrast, anionic ligands such as Cl^- and F^- lead to the formation of five-coordinate high-spin ($S = 5/2$) complexes. Maltempo discussed a spin-admixed $S = 3/2$, 5/2 state on the basis of quantum mechanical calculations, and suggested that the $S = 3/2$ state is an important contributor to the spin state of certain bacterial heme proteins known as cytochromes c'.[2]

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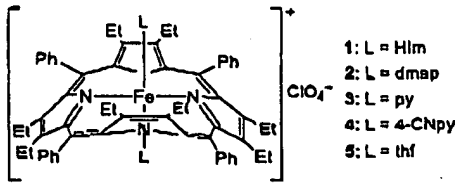
We and others recently reported that highly nonplanar (porphyrinato)iron(III) complexes with weak axial ligands show a quite pure intermediate spin state.[3, 4] The results were ascribed to the short $Fe-N_{por}$ bonds of the nonplanar porphyrin rings and the weak coordination ability of the axial ligands.[5] We therefore expected that the spin state of nonplanar $[Fe^{III}(oetpp)L_2]ClO_4$ (1–5) could change from



$[Fe(Oetpp)L_2]ClO_4$

the pure $S = 1/2$ to the pure $S = 3/2$ state as the axial ligand changes from strong HIm to weak THF; the order of the coordination ability is HIm > dmap > py > 4-CNpy > thf.[6] Of particular interest are the spin states of 2–4 because the axial ligands of these complexes are ranked between HIm and THF.

Table 1 lists the Mössbauer parameters, isomer shift (IS; relative to α-iron foil at 290 K), and quadrupole splitting (QS) measured at ambient and liquid nitrogen temperatures. The QS values for **1** and **2** at ambient temperature were within the range of low-spin complexes.[7] The IS and QS values for **4**

Table 1. Mössbauer parameters and spin state (S) of 1–5.

		T (K)	IS ($mm\,s^{-1}$)	QS ($mm\,s^{-1}$)	Γ_1 ($mm\,s^{-1}$)	Γ_2 ($mm\,s^{-1}$)	S
1		297	0.18	1.82	0.24	0.25	1/2
		78	0.26	1.86	0.40	0.62	1/2
2		290	0.19	2.21	0.27	0.32	1/2
		80	0.26	2.31	0.55	0.89	1/2
3		290	0.32	2.76	0.27	0.29	3/2–1/2
		80	0.25	2.29	0.47	0.64	1/2
4	site A	295	0.37	3.26	0.32	0.33	3/2
	site A	80	0.57	3.03	0.47	0.47	3/2
	site B	80	0.20	2.70	0.64	0.64	1/2
5		290	0.41	3.65	0.32	0.26	3/2
		80	0.50	3.50	0.77	0.49	3/2

(0.37 and 3.26 $mm\,s^{-1}$, respectively) were close to those for **5** (0.41 and 3.65 $mm\,s^{-1}$); **5** has been fully characterized as the quite pure intermediate-spin complex.[4] Thus, from the viewpoint of Mössbauer spectroscopy, **1** and **2** are the low-spin complexes, while **4** is the intermediate-spin complex at ambient temperature. Figure 1 shows the Mössbauer spectra of **3** and **4** taken at ambient temperature and 80 K. The features change as the temperature is lowered. Complex **4** exhibited a new doublet (site B) below 230 K, and the relative intensities for this site increased on decreasing the temperature. The values for sites A and B are in the range of intermediate-spin and low-spin complexes, respectively, and both spin states co-exist at low temperature. This observation implies the occurrence of a novel spin-crossover process [Eq. (1)].[8, 9]

$$\text{low spin } (S = 1/2) \rightleftharpoons \text{intermediate spin } (S = 3/2) \quad (1)$$

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